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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/296,264	04/22/1999	JIM A. WRIGHT	032396-043	8152

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	33

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

App

Office Action Summary

Application No.	Applicant(s)
09/296,264	Wright et al.
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 18, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above, claim(s) *20-22 and 26-29* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-19, 23-25, and 30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Apr 8, 2003* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed June 18, 2003, Paper No. 31.

Claims 1-30 are pending in the instant application, claims 20-22, 26-29 have been withdrawn from prosecution as requested in the amendments filed June 18, 2003, Paper No. 31.

Any rejections not repeated in this Office action are hereby withdrawn.

Response to Arguments and Amendments

Maintained Rejections

Claims 6-16, 23-25 and 30 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office action mailed January 15, 2003, Paper No. 28.

Applicant's arguments filed June 18, 2003 have been fully considered but they are not fully persuasive. Applicants argue that the full scope of the claims are enabled because several existing antisense have reached clinical trials for a variety of indications, including leukemia, AIDS, Crohn's disease, and therefore the instant antisense are also enabled for inhibiting cancer cell or tumor growth or metastasis in vivo, as well as for inhibiting neovascularization in vivo. Contrary to Applicants' assertions, the success of other antisense, targeting other genes that have been found to participate in other diseases or conditions, to reach and inhibit the appropriate target gene whereby treatment effects are provided, is not necessarily predictive of the ability of a

completely different antisense to target its corresponding target gene in the appropriate target cells in vivo, and provide treatment effects.

The instant disclosure is enabling for the in vitro inhibition of human cancer cell growth comprising the administration of antisense oligonucleotides between 15 and 100 nucleobases in length, which specifically target and inhibit the expression of SEQ ID NO: 33, encoding human neuropilin. The instant disclosure is also enabling for the inhibition of human colon tumor growth in vivo comprising the administration of antisense oligonucleotides between 15-100 nucleotides in length that specifically target and inhibit the expression of SEQ ID NO: 33, as well as being enabled for the inhibition of metastasis of melanoma in vivo comprising the administration of these antisense. The instant disclosure is not enabling for the inhibition of neovascularization comprising the administration of these antisense, however. The ability to inhibit target tumor cell growth or metastasis is not predictive of the ability to inhibit neovascularization. Therefore, the scope of enablement rejection is maintained.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al and Soker et al, the combination in view of Milner et al and Baracchini et al.

The claims are drawn to methods and compositions comprising antisense oligonucleotides (including vectors that contain antisense sequences) that specifically target and inhibit the expression of SEQ ID NO: 33, encoding human neuropilin, in vitro, and which antisense comprise one or more phosphorothioate internucleotide linkages, and which antisense are in pharmaceutical compositions, and which methods comprise the inhibition of appropriate target cancer cell growth in vitro comprising the administration these antisense.

He et al teach the nucleotide sequence encoding SEQ ID NO: 33, human neuropilin (See entire document, especially first full paragraph on right on page 740; figure 3 on page 743; second full paragraph on left on page 748; and accession number AF018956).

Soker et al teach the correlation between high human neuropilin (a.k.a. $VEGF_{165}$) expression and cancer cell growth (See especially the text on pages 5761-5762).

The primary references do not teach antisense oligonucleotides that target and inhibit the expression of SEQ ID NO: 33 encoding neuropilin in vitro, nor pharmaceutical compositions comprising these antisense, nor the incorporation of phosphorothioate internucleotide linkages into antisense.

Milner et al teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence (See especially figures 5-7 on pages 539-540).

Baracchini et al teach the administration of pharmaceutical compositions comprising antisense oligonucleotides to appropriate cells in vitro to inhibit target gene expression and target cell growth, as well as teaching the incorporation of phorphorothioate internucleotide linkages into antisense oligonucleotides (See col. 6, 17 and 18).

It would have been obvious to one of ordinary skill in the art to inhibit the expression of SEQ ID NO: 33 using antisense oligonucleotides in vitro because the nucleotide sequence of human neurilin had been taught previously by He et al and the methods for inhibiting a target gene of known sequence using antisense had been taught previously by Milner et al, and one of ordinary skill in the art would have expected that antisense between 15 and 100 nucleobases that are targeted to SEQ ID NO: 33 would inhibit its expression in vitro. It would have been obvious to one of ordinary skill in the art to incorporate phorphorothioate internucleotide modifications

into the antisense oligonucleotides because Baracchini teach the incorporation of such modifications into oligonucleotides and one of ordinary skill in the art would expect such modifications to enhance antisense stability and target binding, as taught by Baracchini et al. Milner et al additionally have taught methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have been motivated to inhibit the expression of human neuropilin of SEQ ID NO: 33 because this gene has been implicated in the proliferation of cell growth, including cancer cell growth, as taught previously by Soker et al. It would been obvious to administer a vector encoding antisense targeting human neuropilin to inhibit the target gene's expression because incorporation of a nucleotide sequence into an appropriate vector for expression in a target cell is routine in the art and one would expect that an appropriate vector would allow for expression of the antisense sequence within the target cell, leading to target gene inhibition in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, would successfully be used for the in vitro inhibition of expression neurilin and consequently for the in vitro inhibition of target cell growth, because this gene has been implicated in target cell proliferation, and Baracchini et al have taught the inhibition of target cell growth following target gene inhibition by antisense in pharmaceutical compositions. One of ordinary skill in the art would have been motivated to incorporate

phosphorothioate internucleotide linkages into antisense oligonucleotides because such modifications are known to increase antisense stability, as taught by Baracchini et al.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of "additional nucleotides not complementary to the neuropilin mRNA" cannot be determined in claim 2, lines 2-3. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 23-25 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising the administration of antisense oligonucleotides, or analogs thereof, that target SEQ ID NO: 33, or optionally further comprising additional nucleotides not complementary to SEQ ID NO: 33.

The specification and claims do not indicate the distinguishing attributes that are concisely shared by the members of the genus comprising analogs of antisense oligonucleotides, nor of additional nucleotides that not complementary to SEQ ID NO: 33. The disclosure does not describe the elements that are essential to the genus comprising antisense oligonucleotides or analogs thereof. Thus, the scope of the claims includes numerous structural variants and genera are highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures of compounds within these genera from others are missing from the disclosure. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed. Applicant was therefore not in possession of the claimed genera.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

August 24, 2003